PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT-2660	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/07260	International filing date *(day/month/year)* 04.07.2003	Priority date *(day/month/year)* 09.08.2002
International Patent Classification (IPC) or both national classification and IPC C07K7/06		
Applicant YAMANOUCHI EUROPE B.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.03.2004	07.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Mauhin, V Telephone No. +49 89 2399-7027

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07260

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-23 as originally filed

Claims, Numbers

1-27 as originally filed

Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 25,27

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-24,26
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24,26
Industrial applicability (IA)	Yes:	Claims	1-24,26
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 25 concerning a binding molecule capable of specifically binding a compound according to any of claims 1-11 was not searched as said compounds are not sufficiently characterized (See international search report).

Claim 27 is completely unclear and was not searched.

Consequently, no opinion with regard to novelty, inventive step and industrial applicability will be established for claims 25 and 27 (Rule 66.1(e) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO-A-0027420
D2: Blood. United States 15 Nov 2002 (15-11-2002), 100(10), 3570-3577
Prepublished online 5 Jul 2002 (5-07-2002)

1. **Present application**

The present application relates to a compound with affinity to human P-selectin comprising a peptide with an amino acid sequence **X-[EGDF]$_m$-[FW]-[CV]-D-[CV]-Y** where m=0 or m=1 and X and Y are respectively the N-terminal and the C-terminal sides of the sequence, wherein X and Y can be a short amino acid sequence which may be substituted with different chemical groups. Functional equivalents of said compounds are disclosed. The application relates also to methods for the preparation of said compound, the use of said compounds for the manufacture of a medicament and a pharmaceutical composition comprising said compound. Finally, it relates to a method for determining whether a molecule comprises a binding affinity for P-selectin, a binding molecule capable of specifically binding said compound and a method for determining whether a compound is capable of binding to human P-selectin.

2. Novelty (Article 33(2) PCT)

2.1 Claims 1-24 and 26 do not meet the requirements of Article 33(2) PCT.

2.2 Document D1 refers to peptido-mimetics of carbohydrate structures of an adhesion molecule, said adhesion molecule being a selectin (page 6, lines 10-13; page 10, lines 19-21). Said peptido-mimetics can be used for the treatment of cancer in a mammal (page 6, lines 27-29; page 13, lines 6-8; example 14), inflammatory response in a mammal (page 7, lines 3-7; page 13, lines 8-18; page 22, lines 18-23; example 8). They can also be used in a method of identifying a variety of peptido-mimetics of carbohydrate ligands (page 7, lines 8-11; page 23, lines 16-22; page 26, lines 4-13). Said peptido-mimetics can be modified to increase their stability *in vivo*. Such modifications include the incorporation of unnatural amino acids (D configuration), the incorporation onto the N-terminus or the C-terminus of the peptide of a moiety which can include straight chain, branched, cyclic or heterocyclic alkyl groups, straight chain, branched, cyclic or heterocyclic alkanoyl groups, a positively charged reporter group and/or one up to 15 additional amino acids independently selected from L- or D- configuration optionally substituted with straight chain, branched, cyclic or heterocyclic alkyl groups, straight chain, branched, cyclic or heterocyclic alkanoyl groups, a positively charged reporter group. These peptides may also be modified to cyclize the peptide by joining the N- and C- termini of the peptide. Additional amino acids or spacers may be introduced into the peptides (page 13, line 14- page 15, line 27). The peptides can be prepared conventionally by resort to known chemical synthesis techniques, e.g., solid-phase chemical synthesis or by known recombinant DNA techniques (page 16, line 25 - page 17, line 13). The peptido-mimetics are formulated into pharmaceutical compositions suitable for administering to a mammalian subject, preferably a human (page 17, lines 15-17). Hence, according to the definition of a **functional equivalent** in the description of the present application (page 10, lines 17-20), all the peptido-mimetics disclosed in D1 are **functional equivalents** of the compound disclosed in the present application.

Thus, claims 1-24 do not fulfill the requirements of Article 33(2) PCT.

2.3 Document D2 was prepublished online on the 5th of July 2002 (i.e. before the priority date of the present application) and is therefore considered as included in prior art. D2 refers to peptide ligands that are specific for human P-selectin and that inhibit the interaction between P-selectin and P-selectin glycoprotein ligand 1 (page 3570, Introduction; page 3571, Results- Screening of phage displayed peptide libraries

against human P-selectin). A consensus peptide motif [ED][WF][VC]DV is disclosed as well as the optional presence of amino acids at the N- and C-termini and constrained forms of the peptides (table 1; page 3572, Results- Screening of phage displayed peptide libraries against human P-selectin). The better affinity of a tetrameric complex is also shown (page 3573, Results- Blocking of P-selectin-mediated cell adhesion by synthetic peptides; page 3576, Discussion- last paragraph). The peptides were generated by recombinant DNA technology or synthesized by standard solid-phase methods (pages 3570-3571, Material and methods- Phage libraries; Peptides). Said peptides were shown to bind to chimeric P-selectin consisting of human Immunoglobulin G1 fused to the binding domain of human P-selectin, i.e. a binding molecule comprising an antibody or a functional part thereof(page 3571, Results- Screening of phage displayed peptide libraries against human P-selectin). Hence, even if no substitutions at the N- and C- termini are disclosed, according to the definition of a **functional equivalent** in the description of the present application (page 10, lines 17-20), all the peptide ligands disclosed in D2 are **functional equivalents** of the compound disclosed in the present application.

Thus, claims 1-24 and 26 do not fulfill the requirements of Article 33(2) PCT.

3. Inventive step (Article 33(3)PCT)

3.1 Should the applicant overcome the objection raised above concerning lack of novelty by, for instance, restricting the scope of the claims through the deletion of the functional equivalents, claims 1-24 and 26 would still lack an inventive step, for the following reasons:

3.2 The subject-matter of claim 1 differs from the compounds disclosed in the closest prior art document D2 (cf. § 3.2) in that there are substitutions at the N- and/or C-termini. In D2, one of the disclosed compound has a EC_{50} of 2µM (see TM11, page 3574, Table 2).
The problem to be solved by the present invention may therefore be regarded as the provision of compounds which have an affinity to P-selectin.
The solution proposed is a chemical substitution of the compounds disclosed in D2.
In the light of teaching of D1 (cf. § 2.1), it would be obvious for the skilled person to substitute the compounds disclosed in D2 with chemical compounds at the C- and N-termini, arriving to the subject-matter of claims 1-24 and 26.
If one considers as special technical effect a higher affinity to P-selectin, the Examiner agrees with the Applicant with regard to some specific compounds which

show a 100-fold higher affinity to P-selectin. However, said special technical effect and, thus, inventive step, has to concern the whole scope of a claim, which is not the case here, since some derivatives even show a decreased affinity to P-selectin (See tables 1 and 2 of example 4) .

Thus, claims 1-24 and 26 do not meet the requirements of Article 33(3) PCT.

3. Industrial applicability

Claims 1-24 and 26 comply with the requirements of Article 33(4) PCT.